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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/165,522	10/02/1998	ROGER J. DAVIS	10363/005001	7986

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/165,522	DAVIS ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,18,19,23-36 and 46-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,18,19,23-36 and 46-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Claims 1-2, 18-19, 23-36, 46-59 and new claims 60-69 are still at issue and are present for examination. Applicants erroneously indicate that claims 7-17 remain withdrawn in the application while the same were cancelled by applicants in the paper foiled on 3-12-01. Applicants are required to correct this discrepancy in response to this Office action.

Applicants' amendments and arguments filed on 9-18-03 have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 18, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over McKay et al. (US 5,877,309, 3-2-1999, filed 8-13-1997) in view of Gupta et al. (EMBO Journal, Vol. 15(11):2760-2770, 1996) and Sawyer et al., (Molecular Biology and Biotechnology, A comprehensive Desk reference, Ed. Robert A. Myers, 1995, Wiley-VCH, USA pages 648-653). Claims 1-2 of the instant application are drawn to a method of identifying a compound that modulates JNK3 expression. McKay et al. teach a method for assaying modulation of expression of JNK protein including JNK1, JNK2 and JNK3 (see particularly, examples 2-5). McKay et al.

also teach oligonucleotides capable of hybridizing to nucleic acids encoding JNK1-3 and modulating the expression of JNK proteins. Furthermore, McKay et al. teach that such oligonucleotides can be used to for inhibiting hyper proliferation of cells and formation , development and maintenance of tumors. However, McKay et al. do not teach specifically a peptide, peptidomimetic, a small organic molecule or a small inorganic molecule.

Gupta et al. teach the identification of JNK isoforms, including JNK3 from adult human brain cells (neuronal cells) and express such JNK isoforms in CHO cells. The reference teaches that c-Jun is an established substrate for JNK3 and has a kinase activity. The reference of Gupta et al. provides a cDNA for the respective JNK isoforms and assay methods for determining the activity and binding of JNK3 to its substrate.

However, using the reference of McKay et al. in combination with that of Gupta et al. who teach the isolation of JNK3 from brain cells (neuronal cells) it would have been obvious to one of ordinary skill in the art, to identify agents other than oligonucleotides that modulates the expression of JNK3 in neuronal cells, either in order to increase the number of agents that become available for such use or to overcome the disadvantages of the method of using antisense oligonucleotides. For example, it is well known in the art that the method of using antisense oligonucleotides suffers from some inherent drawbacks which include the question of stability of the antisense oligonucleotide. It is well known in the art that oligonucleotides are highly unstable in the serum and inside the cell. Secondly the oligonucleotides must be able to enter or penetrate the cell membranes in this case neuronal cell membranes crossing blood brain barrier, and form a stable Watson-Crick or Hoogesteen complex with complementary target sequences under physiological conditions. It is also well known in the art that in order to make

the oligonucleotides resistant to the action of endogenous 3'-exonucleases and 5'-exonycleases, a number of additional modifications are required (see enclosed reference Uhlmann et al., Molecular Biology and Biotechnology, A comprehensive Desk reference, Ed. Robert A. Myers, 1995, Wiley-VCH, USA pages 38-45, to support the above arguments by the Examiner). On the other hand the use of peptides and peptidomimetics for treatment of disorders involving enzymes and receptors is well known in the art. Examiner asserts that this is not an opinion of the Examiner and provides a publication to support his assertion (see enclosed reference Sawyer et al., Molecular Biology and Biotechnology, A comprehensive Desk reference, Ed. Robert A. Myers, 1995, Wiley-VCH, USA pages 648-653). Among the several advantages of the use of peptides and peptidomimetics, the most recognized in the art appears to be its use as pharmaceutical agents and the very number of modes of administration available for the same. Peptides and peptidomimetics can be administered in many forms, including parenteral, interstitial, oral, nasal and percutaneous. In case of oral administration one reason to chemically transform peptides into peptidomimetic or non-peptide derivatives has been to identify prototypic lead compounds with oral bioavailability, which has already shown success in the development of orally effective ACE inhibitors, rennin inhibitors, HIV protease inhibitors etc. Therefore, one of ordinary skill in the art would have been motivated to identify peptides or peptidomimetics in view of disadvantages of using the oligonucleotides listed above or simply to have an extensive list of compounds in addition to oligonucleotides that could be easy to manufacture, pack, and deliver and or administer to a patient. Furthermore, based on McKay et al. teaching that inhibition of JNK activity (which can be brought about by preventing its expression) results in decreased AP-1 activity leading to inhibition of abnormal cell proliferation

and tumor proliferation, development and maintenance (see column 1, lines 25-30) one of ordinary skill in the art would have been motivated to extend the same type of experiment in neuronal cells to develop methods to overcome neuronal cell proliferation and/or tumor proliferation in brain. One would have a reasonable expectation of success since McKay et al. already demonstrate the modulation of expression of JNK-3 by one of the method and Gupta et al. teach the relevance of JNK-3 in brain and also due to the fact that methods to design peptides or peptidomimetics to modulate the expression are commonly known in the art.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicants have traversed the above rejection arguing that Examiner has not established a *prima facie* case of obviousness. Applicants now appear to have focused their attention on the Gupta et al. reference. Basically, applicants argue that Gupta et al. have isolated the JNK3 from a brain cDNA library which contains the cDNA from not only neuronal cells but from other types of cells such as glia, and therefore it cannot be concluded that Gupta et al. teaches expression of JNK3 in neuronal cells and such a conclusion would constitute impermissible hindsight. As a further support to their argument, applicants have filed a Rule 1.132 declaration by Roger Davis and also a copy of a page from the book "Principles of Neural Science", Kandel and Schwartz (Eds) Elsevier, NY. which indeed states that "there are between 10-50 times more glia cells than neurons in the central nervous system". Examiner acknowledges said submission by the applicants. However, Examiner takes the position that such a declaration and a submission of a reference is still not persuasive to overcome the above rejection for the following reasons. In view of the applicant's submission of

the above reference it can be agreed that it was commonly known and well established in the prior art that "there are between 10-50 times more glia cells than neurons in the central nervous system". Therefore, with such information in hand and the reference of Gupta et al. in hand, it would have been obvious to those skilled in the art to verify the teachings of Gupta et al. further, and confirm whether JNK3 was expressed in neuronal cells or non-neuronal cells in the central nervous system or the brain in particular. Examiner has taken that position in view of other references in the art such as that of Martin et al. (Molecular Brain Res., 1996, Vol. 35:47-57) who have indeed reported the neuronal expression of $p49^{3F12}$ by conducting immunochemistry and *in situ* hybridization experiments (see Fig. 1 and 5) and which protein has indeed been referred to as JNK3 by others in the art (for example see Kuan et al., PNAS, 2003, Vol. 100(25):15184-15189, used here as an evidentiary reference). Therefore contrary to applicants argument, the conclusion by the Examiner that the Gupta et al. reference teaches neuronal expression of JNK3 is not due to any hindsight. Furthermore it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Therefore, all arguments by the applicants to negate the value of Gupta et al. reference is moot. Examiner continues to maintain the rejection.

Claims 49-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gupta et al. (EMBO Journal, Vol. 15(11):2760-2770, 1996) and McKay et al. (US 5,877,309, 3-2-1999, filed 8-13-1997) (Rejection is reiterated from previous office action) . Claims 49-59 of the instant application are drawn to a method of identifying candidate compounds for treatment of disorder related to excitotoxicity or a neuronal disorder by simply incubating JNK3 protein with JNK3 substrate (such as c-Jun) and comparing the activity (interaction) of JNK3 in the presence and absence of the compound wherein a difference in the level of JNK3 activity indicates that the compound is a candidate compound.

Gupta et al. teach the identification of JNK isoforms, including JNK3. The reference teaches that c-Jun is an established substrate for JNK3 and has a kinase activity. The reference of Gupta et al. provides assay methods for determining the activity and binding of JNK3 to its substrate. The reference does not teach the use of the same methods towards identification of compounds that modulate the activity. McKay et al. teach a method for assaying modulation of expression (which ultimately leads to reduced activity of JNK3) of JNK protein including JNK1, JNK2 and JNK3 (see particularly, examples 2-5) using oligonucleotides. Furthermore, McKay et al. teach that such oligonucleotides can be used for inhibiting hyperproliferation of cells and formation, development and maintenance of tumors. McKay et al. also teach that one of substrate of JNK3 protein is c-Jun. However, McKay et al. do not teach specifically the use of their methods for identification of a peptide, peptidomimetic, a small organic molecule or a small inorganic molecule.

Using the reference of Gupta et al. which teaches assay methods for JNK3 activity and combining it with McKay et al. which teaches that inhibiting the expression of JNK3 (which

ultimately leads to reduced activity of JNK3) leads to inhibition of hyperproliferation of cells and formation, development and maintenance of tumors, it would have been obvious to one of ordinary skill in the art, especially those interested in identifying agents other than oligonucleotides, to use the assay methods provided by either of the above two references to identify compounds that interact with JNK3 (either by inhibiting expression or activity such as phosphorylation of JNK substrate or by binding to JNK3). One of ordinary skill in the art would have been motivated to do so in view of common knowledge in the art that the oligonucleotides used as antisense is not always successful or even economical or simply to have an extensive list of additional compounds that could be easy to manufacture, pack, and deliver and or administer to a patient maintaining a tumor. Furthermore, McKay et al. teach that one of ordinary skill in the art would be motivated to do this as inhibition of JNK activity (which can be brought about by preventing its expression/activity) results in inhibition of abnormal cell proliferation and tumor proliferation, development and maintenance (see column 1, lines 25-30). One would have a reasonable expectation of success since McKay et al. demonstrate that it is possible to achieve above results by using antisense oligonucleotides.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

Examiner has rejected the above claims under 35 U.S.C. 103(a) over McKay et al. and Gupta et al. because, while the preamble claims 49-52 recite method of identification of candidate compounds for treatment of an excitotoxic disorder (or neuronal disorder), the steps of the claimed method are all directed to identification of compounds which either alter the activity or expression of JNK3, and the intended use of such compounds, once identified, does not carry

any patentable weight, as the steps of the method are identical regardless of what one intends to use the selected compounds for, in the future. Furthermore, applicants may argue that the above rejection is improper as the reference of McKay et al. or Gupta et al. does not teach the involvement of JNK3 in neuronal disorders or that compounds which modulate activity/expression of JNK3 can be used to treat neuronal disorders. Such an argument will not be persuasive to overcome the above rejection because applicants have not established any specific step of the claimed method that requires knowledge of such a relationship between JNK3 and neuronal disorders or JNK3 and excitotoxic disorders in the claims. Applicants appear to claim that any compound that simply modulates the activity/expression or interacts with JNK3 protein and its substrates is a candidate compound for treating neuronal disorders or excitotoxicity.

Claims 23-36, 46-48 and 60-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gupta et al. (EMBO Journal, Vol. 15(11):2760-2770, 1996), Schwarzschild et al. (J. Neuroscience, May 1997, Vol 17(10):3455-3466) and Meldrum B (Brain Research Reviews, 1993, Vol. 18:293-314). Claims 23-36 and 46-48, 60-69 are drawn to a method of identifying a compound that modulates JNK3 expression, activity, binding to a substrate or phosphorylation of JNK3 substrate wherein the method comprises incubating a cell exhibiting JNK3 expression/activity/binding to its substrate/phosphorylating its substrate with a compound under conditions and for a time sufficient to exhibit the respective function absent the compound, incubating a control cell under the same conditions and for the same time absent the compound, measuring said function in the presence and absence of the compound, comparing the amount of

said JNK3 function in the presence and absence of the compound, selecting the compound if there is a difference in the level of said function in the presence and absence of the compound and administering the selected compound to an animal model of an excitotoxic disorder and assaying the animal for excitotoxicity, wherein a decrease in excitotoxicity in the animal indicates that the compound modulates said function, wherein said functions are decreased, wherein the animal model is mouse model, wherein the excitotoxic disorder is kainic acid induced or pentetrazole-induced disorder.

The reference of Gupta et al. has already been discussed above. Gupta et al. teach the isolation of nearly 10 different isoforms of JNK proteins from human brain cDNA library and subclone those cDNAs in CHO cells. The reference also teaches the isolation and characterization of JNK1, JNK2 and JNK3 and specific assays for activity (result of expression of JNK), assays to determine binding of the substrate and phosphorylation of the substrate. However, the reference does not teach method to identify compounds that modulate the above activities using the very same assays or the role of JNK3 in excitotoxicity..

Schwarzschild et al. teach the role of glutamate in its stimulation of JNK proteins in striatal neurons. The reference teaches that glutamate, which is well recognized in the art as an excitatory amino acid raises the levels of phosphorylated JNK , in other words activates JNK kinases which is mediated via NMDA receptors. The reference also reports the involvement of JNK pathway in glutamate-regulated developmental, neurodegenerative and neurotoxin processes in the CNS. Thus Schwarzschild et al. link glutamate stimulation with activation of JNK kinases. The reference dos not specifically recite that JNK3 is activated. However, Examiner takes the position that all JNK isoforms are encompassed in the above reference.

Meldrum teaches in detail amino acids that act as excitotoxins and their contribution to neurodegenerative disorders. On page 304 the reference provides *in vivo* studies of excitotoxicity and provides different techniques and methods of monitoring excitotoxic effects. Under retinal pathology method, the reference teaches a mouse model (neonatal mice) using high doses of glutamate. The references also teaches the toxicity caused by kainic acid which for all practical purposes is highly similar to glutamate in its excitotoxicity (see page 297).

Combining the teachings of the above three references it would have been obvious to one of ordinary skill in the art that glutamate is an excitotoxin capable of inducing several types of neuronal damage and over stimulation by high levels of glutamate would also activate JNK kinase including JNK3 which phosphorylates other transcriptional factors and therefore, compounds which inhibit JNK activities such as phosphorylation, binding etc. would in turn inhibit excitotoxic effects of glutamate or related amino acids and that such compounds could be identified by administering a compound which inhibits JNK3 expression/activity *in vitro*, to an animal model of excitotoxic disorder as taught by Meldrum and choosing those that reduce the excitotoxic effects. One of ordinary skill in the art would have been motivated to do so as such identified compounds would be expected to have use as therapeutic agents for excitotoxic disorders. One of ordinary skill in the art would have a reasonable expectation of success since Meldrum teach the animal model experiments, Gupta et al. teach the assay methods to monitor for JNK activity/expression/binding and phosphorylation and Schwarzschild et al. show the connection between glutamate and JNK.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to both the above rejections, applicants argue as if all the references recited by the Examiner teach all the limitations of the claims in question. However, Examiner would like to point out that if all the references has taught all the limitation of the claims then the reference would have been used to reject the claims under 35 U.S.C. 102 statutes as opposed to their use in an obviousness rejection. Here again applicants main thrust of their arguments appears to be that Gupta et al. reference does not teach the expression of JNK3 in neuronal cells. However, applicants arguments are not persuasive as Examiner continues to maintain that Gupta et al. reference renders above claims and all other claims obvious not alone but in combination of the references cited therewith.

Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao Ph.D.
12/21/03